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Cost Analysis of Implementing Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry Plus Real-Time Antimicrobial Stewardship Intervention for Bloodstream Infections

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ABSTRACT Studies evaluating rapid diagnostic testing plus stewardship intervention have consistently demonstrated improved clinical outcomes for patients with bloodstream infections. However, the cost of implementing new rapid diagnostic testing can be significant, and such testing usually does not generate additional revenue. There are minimal data evaluating the impact of adding matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) for rapid organism identification and dedicating pharmacy stewardship personnel time on the total hospital costs. A cost analysis was performed utilizing patient data generated from the hospital cost accounting system and included additional costs of MALDI-TOF equipment, supplies and personnel, and dedicated pharmacist time for blood culture review and of making interventions to antimicrobial therapy. The cost analysis was performed from a hospital perspective for 3-month blocks before and after implementation of MALDI-TOF plus stewardship intervention. A total of 480 patients with bloodstream infections were included in the analysis: 247 in the preintervention group and 233 in the intervention group. Thirty-day mortality was significantly improved in the intervention group (12% versus 21%, $P < 0.01$), and the mean length of stay was reduced, although the difference was not statistically significant (13.0 ± 16.5 days versus 14.2 ± 16.7 days, $P = 0.44$). The total hospital cost per bloodstream infection was lower in the intervention group ($42,580 versus $45,019). Intensive care unit cost per bloodstream infection accounted for the largest share of the total costs in each group and was also lower in the intervention group ($10,833 versus $13,727). Implementing MALDI-TOF plus stewardship review and intervention decreased mortality for patients with bloodstream infections. Despite the additional costs of implementing MALDI-TOF and of dedicating pharmacy stewardship personnel time to interventions, the total hospital costs decreased by $2,439 per bloodstream infection, for an approximate annual cost savings of $2.34 million.

KEYWORDS antimicrobial stewardship programs, bloodstream infections, financial impact, rapid tests

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Timely administration of appropriate antimicrobial therapy is widely recognized as a critical component of the management of septic patients with bloodstream infections (BSIs) (1, 2). Organism identification is a known precursor to the initiation of definitive optimal therapy, and the advent of rapid diagnostic technologies has revolutionized the way that clinical microbiology laboratories identify pathogens. Matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) uses mass spectrometry

to rapidly identify species of bacteria and yeast following isolation from clinical specimens (3). Use of this technology significantly reduces the time to organism identification by 24 to 36 h compared to conventional techniques (4, 5).

Collaboration between the clinical microbiology laboratory and an antimicrobial stewardship program (ASP) is essential when integrating MALDI-TOF into clinical practice. Several studies have evaluated the impact of this technology on clinical outcomes (6–11). Although early evidence suggests significantly improved appropriate antimicrobial therapy even without stewardship intervention, further improvement in clinical outcomes is seen when real-time review of MALDI-TOF results and subsequent intervention are implemented (6, 7). Perez and colleagues were the first to demonstrate that improved clinical outcomes can be achieved when the use of MALDI-TOF is combined with ASP intervention in patients with Gram-negative BSIs. A significant reduction in hospital length of stay was observed in the intervention group (9.3 $\pm$ 7.6 days versus 11.9 $\pm$ 9.3, $P = 0.01$) (8). Huang and colleagues evaluated the impact of this technology combined with real-time ASP intervention in a larger group of patients, including those with BSIs caused by Gram-negative organisms, Gram-positive organisms, and yeast. Their study revealed a reduction in 30-day-all-cause mortality (12.7% versus 20.3%, $P = 0.021$) and intensive care unit (ICU) length of stay (8.3 $\pm$ 9.0 versus 14.9 $\pm$ 24.2 days, $P = 0.014$) (9).

Although existing evidence has consistently demonstrated significantly improved patient outcomes with the implementation of MALDI-TOF in conjunction with ASP intervention, the implications of this approach for health care costs have not been well established. Thus, the focus of this cost analysis was evaluation of the economic impact of implementing rapid organism identification in combination with an antimicrobial stewardship program in patients with BSIs.

Objective. The objective of this study was to examine the financial impact of MALDI-TOF in combination with antimicrobial stewardship resources on total hospital costs, using data from a study previously published by Huang et al. demonstrating improved clinical outcomes (9). The analysis was conducted from a hospital perspective in patients with BSIs.

RESULTS

A total of 480 patients with BSIs were included in the analysis: 247 in the preintervention group and 233 in the intervention group. The demographics of the patients in the two groups are compared in Table 1. The groups were well matched, with the exception that the preintervention group was slightly older and had a higher incidence of chronic heart and lung disease and a higher rate of health care-associated bacteremia. The intervention group had a higher rate of immunosuppression and a higher rate of community-acquired bacteremia. The isolated organisms responsible for the BSIs are described in Table 2. Organism distributions were generally similar in the two groups. However, there were more patients in the intervention group with methicillin-resistant *Staphylococcus aureus* bacteremia (11.6% versus 4.0%, $P < 0.01$) and more patients in the preintervention group with *Acinetobacter* species bacteremia (2.4% versus 0%, $P = 0.03$). Table 3 displays the various costs of hospitalization for the two groups. The thirty-day mortality rate was significantly reduced in the intervention group (12% versus 21%, $P < 0.01$), and the mean length of stay was reduced, although the difference was not statistically significant (13.0 $\pm$ 16.5 days versus 14.2 $\pm$ 16.7 days, $P = 0.44$), as displayed in Table 4.

The cost of the organism identification methodologies was included for both periods, and the cost of the ASP pharmacist time was included for the intervention period only. In total, the preintervention cost for these items was $5,639, while the cost in the intervention period was $18,362. Despite the increased costs for the MALDI-TOF system and the ASP personnel time, the total hospital cost per bloodstream infection was lower in the intervention group ($42,580 versus $45,019), as illustrated in Table 3. Intensive care unit costs accounted for the largest share of the total costs per blood-

TABLE 1 Demographic characteristics of preintervention versus intervention populations

Patient population demographics	Value (s)[a]		
	Preintervention (n = 247)	Intervention (n = 233)	P value
Age, yrs (mean ± SD)	59.8 ± 15.1	56.3 ± 16.6	0.02
Female	103 (41.7)	87 (37.3)	0.35
Comorbidities			
Malignancy	107 (43.3)	99 (42.5)	0.93
Chronic heart disease	107 (43.3)	80 (34.3)	0.05
Chronic kidney disease	58 (23.5)	59 (25.3)	0.67
Chronic lung disease	42 (17.0)	21 (9.0)	0.01
Chronic liver disease	22 (8.9)	30 (12.9)	0.19
Solid-organ transplant	19 (7.7)	25 (10.7)	0.27
Bone marrow transplant	17 (6.9)	20 (8.6)	0.50
HIV	0 (0.0)	0 (0.0)	>0.99
Immunosuppression			
Chemotherapy within 90 days	35 (14.2)	47 (20.2)	0.09
Antirejection medications	34 (13.8)	41 (17.6)	0.26
Chronic corticosteroids	27 (10.9)	38 (16.3)	0.11
ANC[b] < 500 cell/μl	7 (2.8)	12 (5.2)	0.24
CD4 T cells < 200 cells/μl	0 (0.0)	0 (0.0)	>0.99
Clinical status			
ICU admission	91 (36.8)	78 (33.5)	0.45
Hemodynamic instability requiring vasopressor support	29 (11.7)	30 (12.9)	0.78
Source of bacteremia			
Central venous catheter	51 (20.6)	60 (25.8)	0.20
Intra-abdominal region	49 (19.8)	46 (19.7)	>0.99
Genitourinary region	40 (16.2)	36 (15.5)	0.90
SSTI/BJI[c]	26 (10.5)	26 (11.2)	0.88
Respiratory	16 (6.5)	11 (4.7)	0.43
Foreign device	5 (2.0)	6 (2.6)	0.77
Other	9 (3.6)	17 (7.3)	0.11
Unknown	51 (20.6)	31 (13.3)	0.04
Complication			
Endocarditis	9 (3.6)	17 (7.3)	0.11
Metastatic seeding	8 (3.2)	6 (2.6)	0.79
Type of acquisition			
Hospital acquired	87 (35.2)	80 (34.3)	0.85
Healthcare associated	94 (38.1)	65 (27.9)	0.02
Community acquired	66 (26.7)	88 (37.8)	0.01

[a]Data represent number (percent) of patients unless otherwise indicated.
[b]ANC, absolute neutrophil count.
[c]SSTI, skin and soft tissue infection; BJI, bone and joint infection.

stream infection in each group and were also lower in the intervention group ($10,833 versus $13,727 per patient).

DISCUSSION

This analysis evaluated the financial impact of a dual intervention approach utilizing rapid diagnostic testing with MALDI-TOF in conjunction with antimicrobial stewardship pharmacist real-time review following positive blood culture results and demonstrated an annual cost saving of $2.34 million ($2,439 per BSI), in addition to improving all-cause mortality and reducing the length of hospitalization by 1 day. Utilizing stewardship pharmacists to modify therapy following rapid diagnostic results has consistently demonstrated improved outcomes in a large number of studies (8, 9, 11, 12). Additionally, three quasi-experimental studies have previously reported the total hospital costs preceding and following implementation of rapid diagnostic testing plus

TABLE 2 Organism distribution

Organism[a]	No. (%) of patients with indicated infection		*P* value
	Preintervention ($n = 247$)	Intervention ($n = 233$)	
Gram-positive	133 (53.8)	131 (56.2)	0.65
Staphylococcus aureus	32 (13.0)	38 (16.3)	0.30
MSSA	22 (8.9)	11 (4.7)	0.07
MRSA	10 (4.0)	27 (11.6)	<0.01
Streptococcus spp.	24 (9.7)	32 (13.7)	0.20
Enterococcus spp.	30 (12.1)	22 (9.4)	0.38
Enterococcus faecalis	17 (6.9)	12 (5.2)	0.45
Enterococcus faecium	13 (5.3)	9 (3.9)	0.52
VRE	10 (4.0)	8 (3.4)	0.81
Other	47 (19.0)	39 (16.7)	0.55
Gram-negative	100 (40.5)	85 (36.5)	0.40
Escherichia coli	39 (15.8)	32 (13.7)	0.61
Klebsiella spp.	18 (7.3)	23 (9.9)	0.33
Enterobacter spp.	15 (6.1)	7 (3.0)	0.13
Pseudomonas aeruginosa	10 (4.0)	9 (3.9)	>0.99
Acinetobacter spp.	6 (2.4)	0 (0)	0.03
Citrobacter spp.	3 (1.2)	5 (2.1)	0.49
Serratia spp.	1 (0.4)	4 (1.7)	0.20
Achromobacter spp.	1 (0.4)	0 (0)	>0.99
Other	7 (2.8)	5 (2.1)	0.77
Yeast	14 (5.7)	17 (7.3)	0.18
Candida spp.	13 (5.3)	17 (7.3)	0.45

[a]Abbreviations: MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

stewardship intervention (8, 11, 13). Perez and colleagues utilized MALDI-TOF plus stewardship intervention for Gram-negative bacteremia and reported a total hospital cost savings of $19,547 ($45,709 versus $26,162) per bacteremia episode (8). The same authors published a study 2 years later focusing on multidrug-resistant Gram-negative bacteremia and reported a similar cost savings of $26,298 ($78,991 ± $90,106 versus $52,693 ± $83,526) (11). Finally, Bauer and colleagues evaluated rapid organism identification utilizing GeneXpert real-time PCR plus stewardship intervention for patients with *S. aureus* bacteremia and reported a total hospital cost savings of $21,387 ($69,737 ± $96,050 versus $48,350 ± $55,196) (13). All 3 studies reported a reduction in the length of hospitalization, which is likely the main driver of costs savings, but minimal information was provided regarding the calculation of the cost savings from these studies. Bauer and colleagues reported that the total hospital costs were derived from reported total hospital costs from the pharmacy, microbiology laboratory, and room and board cost centers. Both studies by Perez and colleagues determined the cost saving for patients that survived hospitalization, and hospital costs were calculated by adding up the costs incurred across all cost centers, including room and board, pharmacy, radiology, and laboratory.

The cost saving of $2,439 per bacteremia episode reported in this study is significantly lower than the saving reported in the 3 previous studies for several reasons. First, it appears that the cost of implementing rapid diagnostic testing and the cost associated with the pharmacist's time to review and perform intervention were not accounted for in the cost savings in the previous studies; those costs were included in our analysis. Laboratory costs are typically derived from procedure codes (Current Procedural Terminology [CPT] codes) and represent a fixed patient cost for organism identification, regardless of whether or not more-expensive rapid diagnostic testing is utilized. Thus, the extra institutional costs for implementing rapid diagnostic technology to identify an organism are not reflected in the inpatient cost figures and were not accounted for in the prior studies. Second, this analysis included patients with any type

TABLE 3 Costs associated with both preintervention and intervention groups

Parameter	Cost ($) per patient[a]		
	Preintervention (n = 233)	Intervention (n = 247)	P value
Cost accounting system			
ICU	13,783 (41,235)	11,023 (24,666)	0.279
Acute care	9,977 (12,463)	9,901 (11,050)	0.566
Pharmacy	5,172 (14,743)	5,501 (10,388)	0.169
Respiratory/pulmonary	3,211 (9,158)	3,139 (10,409)	0.435
Blood procedures	2,724 (11,346)	3,399 (9,987)	0.005
Laboratory	2,188 (4,671)	1,998 (2,537)	0.182
Imaging service	2,177 (3,815)	2,155 (3,514)	0.337
Operating room	1,407 (5,529)	1,790 (7,435)	0.771
Cardiac services	929 (4,740)	924 (5,274)	0.179
Emergency service	698 (1,693)	910 (2,150)	0.851
Anesthesia	224 (813)	207 (574)	0.512
Nephrology	690 (2,463)	958 (2,667)	0.266
Other[c]	1,816	596	NS[d]
Total[b]	44,996 (88,119)	42,501 (56,604)	0.209
MALDI-TOF device, reagent, and antimicrobial stewardship pharmacist time (intervention period only)	0	79	
Pharmacist time	0	36	
MALDI lease (3 mo)		40	
Isolate identification and personnel costs		3	
Vitek for organism identification (3 mo; preintervention only)[e]	23	0	
Total (cost accounting plus incremental costs for intervention)	45,019	42,580	NS

[a]Data represent means ± standard deviations.
[b]Total, hospital costs obtained from cost accounting system.
[c]Other: clinic medicine (total), clinic surgery (total), medical procedure unit (total), neurosurgery (total), oncology (total), organ transplant (total), other ancillary (total), psychiatry (total), recovery room (total), rehabilitation services (total).
[d]NS, not significant (no individual category cost included in "Other" had a P value of <0.05).
[e]Costs for susceptibility testing in the two periods were assumed to be equal, as Vitek-2 was utilized for susceptibility testing in both periods.

of bacterial or fungal pathogen and reported a 1.2-day reduction in the length of stay, which is a smaller reduction than that reported in previous studies. The 3 previous studies focused on specific pathogens which are known to cause higher rates of mortality and complications and reported larger reductions in lengths of stay of 2.6, 6.2, and 8.0 days (8, 11, 13).

The data for this analysis were obtained from the health system cost accounting system and represent costs from 13 distinct cost centers. Interestingly, although this initiative was spearheaded by microbiology and pharmacy departments, the costs for each of those departments were relatively unchanged. The laboratory costs decreased by $190 per patient before factoring in the additional cost of implementing MALDI-TOF, and the pharmacy costs increased by $329 per patient. It is important for health care administrators to recognize the limitations due to the use of data silos in a cost center

TABLE 4 Clinical outcomes for preintervention group compared to intervention group

Parameter	Preintervention (n = 247)	Intervention (n = 233)	Relative risk reduction (%)	P value
30-day mortality	52 (21)[a]	28 (12)[a]	43	<0.01
Hospital LOS[c] (days)	14.2 ± 16.7[b]	13.0 ± 16.5[b]		0.44

[a]Data represent number (percent) of patients.
[b]Data represent mean ± standard deviation.
[c]LOS, length of stay (length of time of hospitalization blood culture positivity to discharge).

system in considering the impact of implementing rapid diagnostic technology, as the microbiology laboratory costs would increase and the pharmacy costs might not change significantly but the health system could realize greater throughput and decreased overall resource utilization by reducing the length of hospitalization and the use of ICU resources.

The cost analysis performed in this study had potential limitations. First, the cost of implementing MALDI-TOF for blood culture review was estimated to be $27,716 for the 3-month interventional period. At this institution, MALDI-TOF is utilized as the primary method for organism identification for cultures from all sources, and the cost included in this analysis was estimated for blood cultures only and therefore represents a percentage of the total MALDI-TOF costs. Additionally, the cost estimate was based on outcomes from this single-center quasi-experimental analysis, with noted differences in characteristics between groups which may have influenced the length of stay and mortality. Thus, the number of patients with bacteremia and incremental improvements in length of stay and mortality may differ at other institutions.

Additionally, there are several factors in this analysis which ultimately induce a more conservative estimate of cost savings. First, the analysis included the cost of pharmacists and microbiology technologist time, but the level of effort required to implement this initiative could be absorbed within the daily workflow, with no additional full-time equivalent (FTE) needed. Second, our institution is continually close to full capacity, and we did not estimate the additional revenue that could be generated by back-filling hospital beds as a result of the decreased length of hospitalization from this initiative. Lastly, the intervention was associated with a cost savings, despite the fact that we did not account for any yearly inflation in costs over the course of the study. Thus, actual cost savings may be greater if hospitals have a stewardship pharmacist already in position and do not need to hire additional personnel and if beds could be filled as a result of greater throughput. A final limitation of this study was the inability to differentiate the cost saving related to implementation of MALDI-TOF versus review and intervention by pharmacists. Previous studies have demonstrated that clinical outcomes were improved by combining stewardship intervention plus rapid diagnostic testing versus reporting rapid diagnostic results alone (12). Additionally, stewardship teams could not optimize timely antibiotic therapy that improves outcomes without rapid diagnostic testing. Thus, we feel that the optimal approach for management of bacteremia should include rapid diagnostic testing plus stewardship intervention, regardless of the ability to determine which entity contributed to outcomes or cost savings.

Conclusion. Implementing MALDI-TOF with real-time stewardship review and intervention decreased mortality for patients with BSIs. Despite the additional costs of implementing MALDI-TOF and of dedicating pharmacy stewardship personnel time to interventions, the total hospital costs decreased by $2,439 per bloodstream infection, for an approximate annual total cost savings of $2.34 million.

MATERIALS AND METHODS

The data set used in this cost analysis were derived from patients included in the single-center quasi-experimental study (9). In brief, adult patients (≥18 years of age) with a BSI who were hospitalized at the University of Michigan Health System (UMHS) were included in the retrospective cost analysis. The 3-month preintervention period included patients that were hospitalized between September to November 2011 and had organisms identified by conventional methods. They served as a historical control. The patients in the 3-month intervention period were hospitalized from September to November 2012 and had organisms identified by MALDI-TOF, with communication of results to an ASP member. The ASP at UMHS consisted of 2 infectious diseases physicians, 3 infectious diseases pharmacists, and an infectious diseases pharmacy resident.

Patients excluded from the analysis were the same as those excluded from the original clinical-outcome evaluation, including those transferred from an outside hospital, those with a BSI secondary to organisms that were not yet validated for identification by MALDI-TOF at the time of the original study, and those with a positive blood culture with coagulase-negative *Staphylococcus* and other skin flora determined to be a contaminant. A sample from a patient with coagulase-negative *Staphylococcus* identified from one set of cultures when two or more blood culture sets were collected was deemed to represent a contaminant, except in cases of suspected infection, based on the source. The following

organisms were excluded: *Mycobacterium* species, *Nocardia* species, anaerobic organisms, and filamentous fungi. Additionally, due to logistical procedures, the cost accounting system at UMHS was unable to generate evaluations of incurred inpatient costs for a number of patient encounters. There were a few scenarios in which costs associated with the BSI were combined with costs of other encounters, including patients with recent prior admissions, patients admitted from ambulatory care clinics, and patients transferred to and from the subacute rehabilitation facility located within the hospital. Because of the inability to associate an accurate cost with the BSI encounter, 21 patients (9 in the preintervention group and 12 in the intervention group) were excluded from the analysis.

Preintervention period. During the preintervention period, the microbiology laboratory personnel contacted the medical team (attending physician, house staff, or midlevel provider) to communicate blood culture positivity immediately following Gram stain results. There was no real-time process for providing notification to the medical team following organism identification or susceptibility results, and there was no real-time notification provided to pharmacists for Gram stain, organism identification, or susceptibility results. The clinical pharmacists reviewed culture results Monday through Friday during day shifts and helped optimize antibiotic therapy, but the process was not a real-time method. Additionally, the ASP may have helped optimize therapy if a patient was on treatment with a restricted antibiotic that prompted the stewardship team to review the patient.

During the preintervention phase, it was assumed that Vitek-2 (bioMérieux, Durham, NC) was used for organism identification and susceptibility testing for all isolates. We assumed one identification per patient for the purposes of the cost analysis since our practice is not to do a full identification for subsequent positives detected within 3 days of the initial positive organism. The assigned Vitek-2 cost of $22.83 per blood culture isolate was based on the ratio of blood isolates to non-blood isolates relative to the cost of the Vitek-2 ($1,488/month instrument lease attributable to bloodstream infections, assuming that one-third of all tests were for blood cultures and $4.76/isolate for reagents and personnel). Thus, the cost of Vitek-2 reported in this analysis represents a fraction of the total cost which is attributed to blood culture isolates and does not represent the total cost of Vitek-2.

MALDI-TOF with stewardship intervention period. The real-time notification of positive Gram stain results to the medical team continued during the intervention period, and the role of clinical pharmacists in reviewing daily culture results was unchanged during the two periods. However, the role of the ASP was modified to include three real-time notifications provided between 6:00 a.m. and 11:30 p.m. 7 days per week for each blood culture at three time points: following positive Gram stain, following organism identification, and following determination of antibiotic susceptibilities. Results reported between 11:30 p.m. and 6:00 a.m. were reviewed the following morning. Prescribers were contacted with established, evidence-based antibiotic recommendations in accordance with institutional guidelines. Interventions made by the ASP are described in the evaluation of the original clinical outcomes (9) but can be broadly classified as broadening or initiating coverage, narrowing antimicrobial coverage to target the isolated organism, discontinuing therapy intended for treatment of targeting organisms that were not isolated, or other.

During the intervention period, MALDI-TOF (Bruker Daltonics, Billerica, MA) was used for organism identification for all isolates recovered from positive blood cultures. Positive blood cultures were subcultured to solid media and incubated overnight. Isolates were then processed by either direct transfer or manual formic acid extraction procedures as recommended by the manufacturer. Vitek-2 was used for susceptibility testing, and as a result, the Vitek-2 costs for susceptibility testing performed in the two periods were assumed to be equal. The incremental operational costs were based on the cost of MALDI-TOF plus ASP pharmacist time compared to the cost of Vitek-2 for identification alone. This was calculated based on the actual lease costs for the device plus the supply and personnel costs for isolate identification for each technology. Similarly to the methods used to assign the cost per isolate associated with Vitek-2 in the preintervention period, the assigned cost of $41.30 to perform organism identification per blood culture isolates is proportional to the total costs of performing testing for all isolates and does not represent the total cost of implementing MALDI-TOF ($3,118/month instrument lease cost attributable to bloodstream infections plus $1.16/isolate personnel cost). In addition, the cost of clinical pharmacist time to follow up on the MALDI-TOF results was included in the intervention group calculations by assuming a cost of $75/h and 30 min for review and intervention for each patient.

Outcomes. Clinical outcomes, including 30-day mortality and hospital length of stay, were calculated for the two groups. Total hospital costs were also compared, consisting of the data from the hospital cost accounting system plus the estimated cost of the MALDI-TOF plus ASP pharmacist time compared to that of the preintervention approach of Vitek-2 alone.

Incurred costs were totaled from the date of BSI to the date of discharge or date of death for adult patients with BSI. Cost data were obtained from the Enterprise Performance Systems, Inc. (EPSi; Allscripts, Chicago, IL), cost accounting system at the University of Michigan Health System. Fixed direct, variable direct, and fixed indirect costs were reported for all patient care activities and categorized by individual clinical groups. The process for total cost determination by this system remained unchanged during the study period.

Statistical analysis. Appropriate descriptive statistics were used to analyze all demographic data. All dichotomous variables were analyzed by Fisher's exact test. Normally distributed continuous variables were analyzed using the 2-tailed Student's *t* test. Continuous variables, including costs that were not normally distributed, were analyzed using the Mann-Whitney U test. A P value of ≤ 0.05 was considered statistically significant.

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